

A Mitochondrial Role in Manganese Toxicity

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Introduction: It has been known for years that intracellular manganese is sequestered by mitochondria; however, the oxidation state of this intracellular and intramitochondrial Mn has not been determined. A knowledge of the oxidation state is important in selecting viable hypotheses on the causes of loss of dopamine in striatal neurons and cell death in the globus pallidus.

Methods and Materials: We carried out our initial 4 days of experimentation in this area (proposal 3795) studying the oxidation state of Mn in liver mitochondria. The experiments compared the XANES absorption spectra of intramitochondrial Mn with those of model compounds. Model compounds used were Mn(II)ATP, Mn(II)HPI, Mn(II)EGTA, Mn(II)Cl₂, Mn(III)Ac, Mn(III)porphyrin, and Mn(IV)O₂.

Results and Conclusions: It has been previously shown that Mn(II) can be oxidized to Mn(III) by reactive oxygen species produced in mitochondria, particularly by superoxide radical. In these experiments we worked over a range of Mn concentration and compared intramitochondrial Mn which had been incubated for only a short time inside the mitochondria with Mn which had been incubated for longer times and with Mn which had been exposed to conditions conducive to superoxide production. The spectra of intramitochondrial Mn were fit to sums of the spectra of the model compounds. The results showed that the best fits (R^2 = over 99) were to combinations of Mn(II)ATP and Mn(II)HPI. Addition of the spectra of other Mn(II) model compounds did not improve the fits. Addition of any of the spectra of Mn(III) or Mn(IV) compounds rapidly degraded the fits under all experimental conditions. This allowed us to conclude that there is no spectroscopic evidence here for stabilization of any Mn(III) compounds inside mitochondria under any of the experimental conditions studied.

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